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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/546,000	06/14/2006	Hirofumi Hamada	50026/054001	8449

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EXAMINER	
HILL, KEVIN KAI	
ART UNIT	PAPER NUMBER
1633	

NOTIFICATION DATE	DELIVERY MODE
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

patentadministrator@clarkelbing.com

Office Action Summary	Application No.	Applicant(s)	
	10/546,000	HAMADA ET AL.	
	Examiner	Art Unit	
	KEVIN K. HILL	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *31 January 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-13 and 15-25* is/are pending in the application.

4a) Of the above claim(s) *1-13,15,18 and 19* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *16,17 and 20-25* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

Detailed Action

Applicant had elected without traverse the invention of Group III, claim(s) 14-17, drawn to a therapeutic composition comprising a genetically modified mesenchymal cell comprising a foreign gene encoding angiopoietin-1.

Within Group III, Applicant has elected the minus-strand RNA viral vector species encoding angiopoietin-1, as recited in Claim 16.

Amendments

In the reply filed January 31, 2008, Applicant has cancelled claim 14, withdrawn claims 1-13, 15 and 18-19, amended claims 16-17, and added new claims 22-25. Applicant's new claims have been entered into the application as requested and will be examined on the merits herein, as they are considered to belong to the elected group.

Claims 1-13, 15 and 18-19 are pending but withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a non-elected invention, there being no allowable generic or linking claim.

Claims 16-17 and 20-25 are under consideration.

Priority

This application is a 371 of PCT/JP04/00957, filed January 30, 2004. Applicant's claim for the benefit of a prior-filed application under 35 U.S.C. 119(e) or under 35 U.S.C. 120, 121, or 365(c) is acknowledged

Acknowledgment is also made of Applicant's claim for foreign priority under 35 U.S.C. 119(a)-(d). The certified copy of JP 2003-040806, filed February 19, 2003 is filed with the instant application.

Accordingly, the effective priority date of the instant application is granted as February 19, 2003.

Information Disclosure Statement

Applicant has filed Information Disclosure Statements on December 17, 2007, January 31, 2008 and March 27, 2008 that have been considered. The signed and initialed PTO Forms 1449 are mailed with this action.

Claim Rejections - 35 USC § 101

1. **The prior rejection of Claims 14 and 16 are rejected under 35 U.S.C. 101 is withdrawn** in light of Applicant's cancellation of claim 14 and amendment to claim 16 specifying that the mesenchymal cell is an **isolated** mesenchymal cell.

Claim Rejections - 35 USC § 112

2. **Claim 16 is rejected under 35 U.S.C. 112, second paragraph, is withdrawn** in light of Applicant's amendment to the claim to clarify that the isolated mesenchymal cell is transfected with a minus-strand RNA viral vector encoding Angiopoietin-1 (Ang-1).

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the Applicant for a patent.
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the Applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the Applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

3. **The prior rejection of Claim 14 under 35 U.S.C. 102(a)** as being anticipated by Nykanen et al (Circulation 107(9):1308-1314, 2003; available online February 17, 2003; *of record in IDS) **is withdrawn** in light of Applicant's cancellation of the claim.

4. **The prior rejection of Claim 14 under 35 U.S.C. 102(b)** as being anticipated by Chae et al (Arterioscler. Thromb. Vasc. Biol. 20(12): 2573-2578, 2000; *of record in IDS) **is withdrawn** in light of Applicant's cancellation of the claim.

5. **The prior rejection of Claims 14 and 17 under 35 U.S.C. 102(a) and 35 U.S.C. 102(e)** as being anticipated by Ueno et al **is withdrawn** in light of Applicant's cancellation of claim 14 and amendment to claim 17 such that the mesenchymal cell is transfected with a minus-strand RNA viral vector encoding Ang-1, which Ueno et al do not disclose.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the Examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the Examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

6. **Claims 16-17 and 20-21 stand, and claims 22-25 are newly rejected under 35 U.S.C. 103(a)** as being unpatentable over Ueno et al (US 2002/0037278 A1) and Sakai et al (FEBS Letters 456:221-226, 1999).

This rejection is maintained for reasons of record in the office action mailed November 1, 2007 and re-stated below. The rejection has been re-worded slightly based upon Applicant's amendment filed January 31, 2008.

Ueno et al disclose bone-marrow derived mononuclear cells [mesenchymal cells] transfected with a nucleic acid encoding Ang-1, wherein said transfected cells may be used in a method of delivering a recombinant nucleic acid molecule to a disease, damaged, ischemic or angiogenic site in a subject by transplantation at or near the site of disease in the context of a pharmaceutically acceptable carrier, e.g. saline (pg 1, [0008]; pg 5, [0042]; pg 8, [0074]). Ueno et al disclose that the nucleic acid molecule encoding the foreign gene may be introduced into the host mesenchymal cell using any one of a genus of viral vectors known in the art (pg 6, [0048]).

Ueno et al disclose that bone-marrow derived mononuclear cells comprise mesenchymal stem cells (pg 4, [0033]), a fact also recognized by Applicant (Specification, pg 22, lines 30-36).

Ueno et al do not disclose the use of a minus-strand RNA viral vector, specifically a Sendai viral vector to deliver the angiopoietin foreign gene to the cell. However, at the time of the invention, Sakai et al taught the development of minus-strand RNA Sendai virus vectors to express foreign genes.

It would have been obvious to one of ordinary skill in the art to substitute the viral vector of Ueno et al with a minus-strand RNA Sendai virus vector as taught be Sakai et al with a reasonable chance of success because the simple substitution of one viral vector for another would have yielded predictable results to one of ordinary skill in the art at the time of the invention. Furthermore, a minus-strand RNA viral vector is not considered an essential feature of the invention in light of the disclosure that the foreign gene encoding Ang-1 may also be delivered via non-minus-strand RNA viral vectors, e.g. an adenoviral vector, an adeno-associated viral vector, a retroviral vector, a lentiviral vector, a herpes simplex virus vector, and a vaccinia virus vector (pg 12, lines 8-10). An artisan would be motivated to use a minus-strand RNA Sendai virus vector to express a foreign gene because Sakai et al teach that Sendai viruses reach a high copy number in infected cells, possesses a broad cellular host range, including non-dividing cells and peripheral mononuclear cells [comprising mesenchymal stem cells], achieve a high level of foreign gene expression, and is extremely useful in producing large quantities of medically important proteins in cells of interest (pg 224, Figure 3B, pg 226, col. 1, ¶2 and col. 2).

Thus, the invention as a whole is *prima facie* obvious.

Applicant's Arguments

Applicant argues that:

a) selection of a minus-strand RNA viral vector, e.g., a Sendai virus vector, in the methods and compositions of the present invention would not have been obvious to one of skill in the art at the time of filing. The specification provides evidence of superior unexpected results using a minus-strand RNA viral vector, resulting in an overwhelming advantage over, e.g., an adenovirus vector in the context of gene transduction into mesenchymal cells. See, e,g., Example 14, pages 51-52 of the English-language specification as filed, entitled "Treatment of limb ischemia using the Ang-l gene-introduced mesenchymal cells." In particular, as shown in Fig. 16, the expression level of the transgene in mesenchymal stem cells infected with a minus-strand RNA viral vector at an MOI of 1 (i.e., one infectious virus particle per cell) was comparable to, or even higher than, that with an adenovirus vector at an MOI of 100. The expression level of the minus-strand RNA viral vector at an MOI of 30 was more than one hundred times higher than that of the adenovirus vector at the same MOI. Accordingly, the specification demonstrates that the gene transduction efficiency of mesenchymal stem cells using a minus-strand RNA viral vector is extraordinarily, and unexpectedly high.

b) the term "angiopoietin-1" appears on page 5 of Ueno as one of about thirty genes enumerated in paragraphs [0042] and [0043]. Ueno provides no working example of a genetically modified mesenchymal cell. Furthermore, Ueno does not demonstrate any effect of Ang-l, or any of the other listed genes, on ischemia when expressed in mesenchymal cells. Without evidence, one skilled in the art could not have predicted whether the Ang-1 expressing mesenchymal cells exhibit a therapeutic effect on ischemia. Specifically, a skilled artisan would not have predicted that the mesenchymal stem cells into which the Ang-l gene was introduced by a minus-strand RNA virus vector shows a significant therapeutic effect on ischemia.

Applicant's argument(s) has been fully considered, but is not persuasive.

With respect to a), as a first matter, the claims are not limited in scope only to mesenchymal stem cells and RNA minus-strand Sendai virus, but also embrace an enormous genus of mesenchymal cell types and RNA minus-strand viruses. Applicant has provided no evidence that the increased transduction efficiency of mesenchymal stem cells would be reasonably extrapolated to the enormous genus of non-stem mesenchymal cell types. Similarly, Applicant has provided no evidence that other RNA minus-strand virus vectors within the claimed genus also demonstrate superior transduction efficiency, nor that mesenchymal [stem] cells transduced with said other minus-strand RNA viruses would also achieve the real-world, clinically meaningful therapeutic effect for treating ischemia. Thus the evidence is not commensurate in scope to the claimed invention.

As a second matter, it appears that Applicant's invention is based upon the discovery of a source of a problem, specifically that the transduction efficiency of mesenchymal stem cells by RNA minus-strand Sendai virus is superior to adenovirus. However, mere recognition of latent properties in the prior art does not render non-obvious an otherwise known invention. *In re Wiseman*, 596 F.2d 1019, 201 USPQ 658 (CCPA 1979). (See MPEP §2145). In the instant case, no evidence has been provided demonstrating that the Sendai virus has been intentionally modified to achieve the observed superior transduction efficiency, nor are such intentional modifications recited in the claims. Rather, the transduction efficiency is a latent property of the Sendai virus, and thus it would naturally flow that the use of a Sendai virus as taught by Sakai et al would necessarily achieve the transfection efficiency observed by Applicant.

As a third matter, obviousness does not require absolute predictability, only a reasonable expectation of success, i.e., a reasonable expectation of obtaining similar properties. See, e.g., *In re O'Farrell*, 853 F.2d 894, 903, 7 USPQ2d 1673, 1681 (Fed. Cir. 1988). In the instant case, the substitution of an adenoviral vector for a Sendai virus vector would provide a reasonable expectation of success. Sakai et al teach that Sendai virus vectors reach quite a high copy number in infected cells, demonstrate efficient replication and gene expression *in vivo*, and hence are extremely useful in producing large quantities of medically important proteins in cells of interest (pg 225, Figure 4; pg 226, col. 1, ¶2).

With respect to b), "the prior art's mere disclosure of more than one alternative does not constitute a teaching away from any of these alternatives because such disclosure does not criticize, discredit, or otherwise discourage the solution claimed..." *In re Fulton*, 391 F.3d 1195, 1201, 73 USPQ2d 1141, 1146 (Fed. Cir. 2004). (See MPEP §2123.) In the instant case, it is unclear how the ordinary artisan, prior to the invention, would be unable to reasonably predict that mesenchymal stem cells into which the Ang-l gene was introduced by a minus-strand RNA virus vector would not show a therapeutic effect on ischemia. At the time of the invention, those of ordinary skill in the art were well aware that Ang-1 would be useful in the treatment of ischemia. Ueno et al is **but one prior art example** teaching the use of Ang-1 for treatment of ischemia. Sakai et al teach that Sendai virus is useful for expressing medically important proteins. Thus, the ordinary artisan, prior to the invention, would reasonably predict that mesenchymal stem cells into which the Ang-l gene was introduced by a minus-strand RNA virus vector would show a significant therapeutic effect on ischemia.

Conclusion

7. No claims are allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the Examiner should be directed to Kevin K. Hill, Ph.D. whose telephone number is 571-272-8036.

The Examiner can normally be reached on Monday through Friday, between 9:00am-6:00pm EST.

If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's supervisor, Joseph T. Woitach can be reached on 571-272-0739. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Kevin K. Hill, Ph.D./
Examiner, Art Unit 1633

/Joseph T. Woitach/
Supervisory Patent Examiner, Art Unit 1633